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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,023	04/02/2004	Salvatore V. Pizzo	5405-304	2746

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
01/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,023	PIZZO ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16-20 and 28-36* is/are pending in the application.

4a) Of the above claim(s) *20 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16-19,28-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/27/10 has been entered.

Status of Claims

2. Claims 14, 16-20 and 28-36 are pending. Claims 20 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims Summary

3. The claims are directed to the administration of an immunogen with Compound 48/80, in a pharmaceutical carrier, to a subject to induce an immune response in the subject. The intended use of Compound 48/80 is as an adjuvant, to enhance the immune response to the immunogen. Claim 16, which depends on claim 14, requires the administration be parenteral. Claims 17-19, which depend on claim 14, require the immune response to be prophylactic, therapeutic and humoral, respectively. Claim 28, which depends on claim 14, requires the administration be mucosal. Claims 29-34 are directed to the method of claims 14, 16, 28, 17-19, respectively.

New claim 36 is directed to a method of providing adjuvant activity by administering Compound 48/80 in combination with an immunogen.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 16-19, 28-34 and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Takesako et al. (U.S. PreGrant Pub No. 2002/0058293 A1, published 05/16/2002, "Takesako") in view of Lenney et al. (Antimicrobial Action of Compound 48/80 against protozoa, bacteria and fungi, Journal of Pharmaceutical Sciences, May 1977, Vol. 66, No. 05, 702-705, "Lenney").

Takesako teaches the administration of an immunogen in a pharmaceutical carrier, to a subject to induce an immune response in the subject. [Example 6-10, in particular.] The administration method disclosed by Takesako includes parenteral and mucosal. Takesako teaches that the immunogen has protective activity, hence, its use as a vaccine composition to induce a prophylactic, humoral and/or cellular immunity. [Paragraph 0148, in particular.]

The vaccine composition of Takesako does not comprise Compound 48/80. However, Takesako suggests the use of antifungal agents and antimicrobial agents with the vaccine. [Paragraph 0148, in particular.]

At the time the invention was made, Lenney teaches an antimicrobial agent that is effective against protozoa, bacteria and fungi. The antimicrobial agent of Lenney is Compound 48/80. [Title and Abstract, in particular.] Thus, it would have been prima facie obvious for one of ordinary skill in the art to use Compound 48/80 as the antimicrobial agent in the vaccine composition of Takesako, since Takesako suggests that any antifungal/antimicrobial agent may be employed. One of ordinary skill in the art would have been motivated to do so to provide antimicrobial protection to the vaccine of Takesako. One would have had a reasonable expectation of success because the addition of antimicrobial agents with pharmaceutical products is routinely practiced, evidenced by Takesako. The particular choice of Compound 48/80 is simply a matter of selecting an agent from those available in the art.

The Office recognizes that neither Takesako nor Lenney teach that Compound 48/80 is useful as an adjuvant, or that the compound will have enhance the immune response to the immunogen. However, the actual steps of administering an immunogen with Compound 48/80 are suggested in the prior art. If one of ordinary skill in the art were to carry out the steps of administering Compound 48/80 with an immunogen, as suggested by Takesako in combination with Lenney, one would have necessarily achieved the adjuvant effect that Applicant asserts is novel. Although Takesako and Lenney did not appreciate the adjuvant effect of Compound 48/80, that does not alter the effect that Compound 48/80 would have when administering it to a subject in combination with an immunogen.

Response to Arguments

5. Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that the claims require an adjuvant-effective amount of Compound 48/80 to be administered to a subject. Applicant notes that since neither Takesako nor Lenney appreciate that Compound 48/80 has adjuvant properties, it would not have been obvious to have used an adjuvant-effective amount of Compound 48/80. Applicant points to McGowen et al. (Vaccine, 2009, 27:3544-3552, "McGowen") as evidence that not all amounts of Compound 48/80 have adjuvant activity. Applicant goes on to state that although Lenney's suggested amount of Compound 48/80 (in an in vitro context) falls within the range of that used in vivo in McGowen, that one would not use the in vitro concentration as guidance for in vivo application.
  - The Office recognizes that neither Takesako nor Lenney teach that Compound 48/80 is useful as an adjuvant, or that the compound will have enhance the immune response to the immunogen. However, the actual steps of administering an immunogen with Compound 48/80 are suggested in the prior art. If one of ordinary skill in the art were to carry out the steps of administering Compound 48/80 with an immunogen, as suggested by Takesako in combination with Lenney, one would have necessarily achieved the adjuvant effect that Applicant asserts is novel. Although Takesako and Lenney did not appreciate the adjuvant effect of Compound 48/80, does not alter the properties that Compound 48/80 would have when administering to a subject in combination with an immunogen. The fact that applicant has recognized

another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See Ex parte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

- In response, the Office has considered the McGowen reference, however, all that the McGowen reference shows is that one must determine the amount of Compound 48/80 that has an adjuvant effect in an animal for a particular antigen. The amount of Compound 48/80 to be used in a composition as an adjuvant, as one of ordinary skill in the art would know, is dependent on the antigen and the subject receiving the composition. No particular range of concentration can be pointed out without further parameters being defined, such as the receiving subject and the antigen. The Office is arguing that one of ordinary skill in the art, using Compound 48/80 as directed by Takesako/Lenney for antimicrobial purposes, would use an amount of Compound 48/80 that falls within the amount required for its use as an adjuvant given the breadth of the claims.
- The Office agrees with Applicant that in vitro results from Lenney regarding the concentration of Compound 48/80 would need to be determined for in vivo applications. Thus, one would not take Lenney's concentrations and directly apply them to a composition to be administered to a subject. Determining the antimicrobial-effective amount to be used when administering to a subject would require further, routine work that can be done by one of ordinary skill in the art.

• Applicant points out that Takesako does not provide working examples or other evidence to support the statement regarding an additive or geometrically enhanced effectiveness of

the combination of immunogen with an antifungal agent (see Takesako, paragraph [0148]). Applicant also argues that some antimicrobial agents may have a detrimental effect on an immune response, evidenced by Fernandez et al. (J. Infect. Dis., 2004, 190:1762-1766, "Fernandez").

- In response to Applicant's argument, Takesako's suggestion to use an antimicrobial agent would be understood by one of ordinary skill in the art to be just that: a suggestion to use an antimicrobial agent. Given that the use of antimicrobial agents is common in the art of vaccines, one would not require experimental results to prove the need for an antimicrobial agent. Although Takesako's expectation of additive or geometrically enhanced effectiveness is not evidenced by experimental data, one would still be motivated to use an antimicrobial agent with the goal of maintaining the integrity of the vaccine composition.
- The Office has considered the Fernandez reference. The Office agrees that not all agents are going to work with every antigen. However, obviousness only requires a reasonable expectation of success. Fernandez does not preclude one from using antimicrobials agents altogether just because some of them have an unwanted effect on the host immune system. Fernandez' teachings merely caution one to consider that such an unwanted effect could be a possible outcome.

- Applicant argues that there is nothing in the cited art or general knowledge in the art delineated by the Examiner to show why one of ordinary skill in the art would have been motivated to select Compound 48/80 out of the thousands of known antimicrobial agents. Applicant argues that one would not have been motivated to use Compound 48/80

because Lenney teaches that the fraction of the compound responsible for antimicrobial activity is not completely separable from the histamine-releasing activity. Applicant argues that because the components of Compound 48/80 have strong mast cell degranulation activity, one would not choose this compound as an excipient in a pharmaceutical product. Further, Lenney discloses that Compound 48/80 only has moderate antimicrobial activity against organisms in general.

- In response to Applicant's argument, the motivation to select Compound 48/80 is simply that Takesako suggests using "other various antibacterial antimicrobial agents" (see paragraph [0148]). Compound 48/80 is a known antibacterial antimicrobial agent, as taught by Lenney. The broad statement supplied by Takesako is the motivation for one of ordinary skill in the art to select any agent known to possess antibacterial antimicrobial activity. Compound 48/80 has the properties that Takesako requires.
- Further, it is understood that Applicant is arguing that Compound 48/80 would not be an attractive adjuvant. Note that the Office has a different reason for combining the references to arrive at the claimed invention. The motivation to combine comes from Takesako's suggestion to use any antimicrobial agent, paired with Lenney's antimicrobial agent which is available and known in the art. Thus, the Office is not taking into account, and does not need to take into account whether one would consider Compound 48/80 to be an adjuvant of interest, but whether one would use Compound 48/80 as an antimicrobial agent.

- Applicant also points to Takeda Chemicals Industries, Ltd. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 83 USPQ2d 1169 (Fed. Cri. 2007). Applicant argues that the findings in Takeda are relevant to the instant claims.
  - In response, the Office has considered Takeda. Takeda is an example of a chemical case in which the Fed Circuit found that the claim was not obvious. In Takeda, one would have had to select a lead compound and further modify the compound to arrive at the claimed invention. There were negative properties known in the art regarding the lead compound, which would have directed one of ordinary skill away from the compound.
  - However, in this case, no further modification of Compound 48/80 is necessary, and there are no negative properties that would lead one away from using the compound. (Note that the Office's reason for combining is different from Applicant's.) As to a "finite number of identified, predictable solutions", Takesako suggests "other various antibacterial antimicrobial agents" (see paragraph [0148]). The fact that there a great number of antibacterial antimicrobial agents does not immediately mean that there is a lack of a finite number of identified, predictable solutions. Takesako teaches that other agents having antibacterial/antimicrobial activity may be used, and Lenney's agent has those particular properties. There is no indication from Takesako that further modification to the antimicrobial agent is required. There is nothing unpredictable concerning the antimicrobial activity of Lenney's agent because Lenney confirms that Compound 48/80 has antimicrobial activity. Therefore, the rejection is maintained for reasons of record.

Conclusion

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stacy B Chen/
Primary Examiner, Art Unit 1648